In re Application of: Michal Amit et al.
Serial No.: 10/581,455
Filed: June 1, 2006
Office Action Mailing Date: September 2, 2009

Examiner: TON, Thaian N
Group Art Unit: 1632
Attorney Docket: 32059

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 52, 55-75 and 78-84 are in this Application. Claims 61-73 have been withdrawn from consideration. Claims 52, 55, 56, 57, 58-60, 74, 75, 78-80, 81, 82, 83, and 84 have been rejected under 35 U.S.C 103 (a). Claims 52 and 74 have been amended herewith. Claim 56 has been cancelled herewith. Claims 85-100 have been added herewith.

Amendments To The Claims

35 U.S.C. § 103 Rejections

Ratcliff et al., 1992, Thomson et al., 1998, US Pat. No. 7,390,659 and Elsea et al., 2002

The Examiner rejected claims 52, 55, 56, 58-60, 74, 75, 78-80 and 82 under 35 U.S.C. 103(a) as being unpatentable over Ratcliff (Transgenic Res. 1:177-181, 1992) when taken with Thomson et al., (Science, 282:1145-1147, 1998) and US Pat. No. 7,390,659, in further view of Elsea et al., (ILAR Journal, 43:66-79, 2002). Specifically, the Examiner states that Ratcliff teach the specific disruption of the cftr gene at the endogenous locus in mouse ES cells by gene targeting; utilizing these mouse ES cells, transgenic animals can be produced to study pathophysiology and testing of new therapeutic drugs. The Examiner admits that Ratcliff does not teach human ESCs or methods of using such in *in-vitro* assays. However, the Examiner asserts that Thomson teach human ESCs, and that genetic modifications could be produced in ES cells, for reducing or combating immune rejection; that Thomson teach that human ESCs can be differentiated, and that human ESCs would be valuable in studies of development and function of tissues that differ between mice and humans, and that screens based upon the in vitro differentiation to specific lineages could identify gene targets for new drugs. The Examiner further states that US Pat. No. 7,390,659 teaches identifying candidate agents for treating conditions associated with motor neuron degeneration using ESCs which contain a mutation in a specific gene. The Examiner states that it would have been obvious to one of ordinary skill in

the art, to utilize the technology to produce specific disruptions in mouse ES cells and apply this technology to human ES cells, and then utilize the resultant cells in methods of screening agents suitable for treating a disorder such as taught by US Pat. No. 7,390,659 with a reasonable expectation of success; and that one of ordinary skills in the art would have been motivated to make this modification in view of Thomson's teachings who suggest producing genetic modifications in ESCs. Examiner's rejection is respectfully traversed. Claims 52 and 74 have been amended herewith. New claims 85-100 have been added herewith.

Applicants point out that a *prima facie* case of obviousness has not been properly set by combining the art of Ratcliff (1992) with that of Thomson (1998), Elsea (2002) and US Pat. No. 7,390,659, since neither of the cited art, nor a combination thereof teach or suggest generating a human embryonic stem cell line carrying a naturally occurring disease-causing mutation in a genomic polynucleotide thereof; or an isolated population of cells consisting of human embryonic stem cells carrying a disease-causing mutation in a genomic polynucleotide thereof as in the currently amended claimed invention.

With respect to Ratcliff (1992) Applicants point that the reference teaches inserting a genetic construct with an hprt minigene (*i.e.*, a non-natural construct) into exon 10 of the mouse CFTR gene (Ratcliff, Page 180, right column, lines 14-17) and not a naturally occurring mutation in the CFTR gene as in the claimed invention. In addition, Applicants point that when Ratcliff et al. introduced the genetic construct into ESCs and generated a chimeric animal, the construct was not expressed in the lung tissue of the chimeric animal (Ratcliff, Page 180, Table 1), the major tissue affected in cystic fibrosis patients, thus Ratcliff et al. failed to teach the generation of a mouse model for a human disease.

Notwithstanding the above arguments, the site directed mutagenesis strategy that was suggested in Ratcliff et al. attempts to introduce a Mendelian mutation (ΔF508 mutation) on a foreign genetic background of a recipient subject. It should be noted that even for Mendelian diseases such as cystic fibrosis, genotype-phenotype correlation analyses show that the genetic background of a subject, e.g., inherited polymorphisms and haplotypes in other genes or loci determine the phenotypic appearance of a specific mutation in terms of severity/complexity of disease (see e.g.,

Castellani C, et al., 2006, attached herewith; Knezevic J et al., 2007, attached herewith). In sharp contrast to the strategy suggested by the cited art, the present inventors uncovered the ultimate cell model of genetic diseases, in which the disease-causing mutations are present on the right genetic background (context), e.g., polymorphisms and haplotypes thereof present in the genome of a human embryo carrying the naturally occurring disease causing mutation.

Thus, one of ordinary skilled in the art in view of the combined teachings of Ratcliff et al. who teach a non-natural genetic construct in mouse ESCs, with Thomson et al., who teach derivation of human ESCs (Thomson, Page 1145, column 2), in view of Elsea et al., who merely state that there is a need for human ESCs as a model for genetic diseases, and US Pat. No. 7,390,659, which teaches methods of inducing differentiation of embryonic stem cells would not have any motivation or expectation of success to generate a human embryonic stem cell line with a naturally occurring disease-causing mutation in a genomic polynucleotide thereof as in the currently amended claimed invention.

In addition, neither of the cited art, nor a combination thereof teach or suggest a population of cells consisting of human embryonic stem cells carrying a disease-causing mutation in a polynucleotide thereof as in New claims 85-100 of the claimed invention.

Withdrawal of the rejection is respectfully requested.

Ratcliff et al., 1992, Thomson et al., 1998, Elsea et al., 2002 and US 2005/0054092

The Examiner has rejected claims 83-84 under 35 U.S.C. 103(a) as being unpatentable over Ratcliff (Transgenic Res. 1:177-181, 1992) when taken with Thomson et al., (Science, 282:1145-1147, 1998) in further view of Elsea et al., (ILAR Journal, 43:66-79, 2002) as applied to claims 52, 55, 56, 58-60, 74, 75, 78-80, 82 above, and further in view of PGPub US 2005/0054092. Specifically, the Examiner states that Ratcliff, Thomson and Elsea which are described above do not specifically teach isolating lineage specific cells by mechanical separation of cells or tissues within the embryoid body, however, US 2005/0054092 teaches that suspension of pPS derived cells can be further enriched with desirable characteristics, such as mechanical separation or cell sorting, such as FACS. Thus, the Examiner states that it would have

been obvious for one of skill in the art to modify the methods taught by Ratcliff, Thomson and Elsea, to include a step of isolating a lineage specific cell as taught by US 2005/0054092 with a reasonable expectation of success, and that one of ordinary skill in the art would have been motivated to make this modification in order to have a purified population of cells for in vitro screening assays. The Examiner's rejection is respectfully traversed. Claim 52 has been amended herewith. New claims 85-100 have been added herewith.

Applicants point out that a *prima facie* case of obviousness has not been properly set by combining the art of Ratcliff (1992) with that of Thomson (1998) in further view of Elsea (2002) and US 2005/0054092, since neither of the cited art, nor a combination thereof teach or suggest generating a human embryonic stem cell line carrying a naturally occurring disease-causing mutation in a genomic polynucleotide thereof; or an isolated population of cells consisting of human embryonic stem cells carrying a disease-causing mutation in a genomic polynucleotide thereof, or cells isolated therefrom as in the currently amended claimed invention.

Withdrawal of the rejection is respectfully requested.

Ratcliff et al., 1992, Thomson et al., 1998, Elsea et al., 2002 and US Pat. No. 5,972,955

The Examiner has rejected claims 57 and 81 under 35 U.S.C. 103(a) as being unpatentable over Ratcliff (Transgenic Res. 1:177-181, 1992) when taken with Thomson et al., (Science, 282:1145-1147, 1998) in further view of Elsea et al., (ILAR Journal, 43:66-79, 2002) as applied to claims 52, 55, 56, 58-60, 74, 75, 78-80, 82 above, and further in view of US Pat. No. 5,972,955. Specifically, the Examiner states that Ratcliff, Thomson and Elsea which are described above do not specifically teach sequences such as those recited in claims 57 and 81, however, US Pat. No. 5,972,955 teaches an exact match of SEQ ID NO:24. Thus, the Examiner states that it would have been obvious for the ordinary skilled artisan to modify the teachings of Ratcliff, Thomson and Elsea to produce human ES cells carrying a mutation such as W1282X as set forth in SEQ ID NO:24, associated with cystic fibrosis, with a reasonable expectation of success. The Examiner's rejection is respectfully traversed. Claim 52 has been amended herewith. New claims 85-100 have been added herewith.

Applicants point out that a *prima facie* case of obviousness has not been properly set by combining the art of Ratcliff (1992) with that of Thomson (1998) in further view of Elsea (2002) and US Pat. No. 5,972,955, since neither of the cited art, nor a combination thereof teach or suggest generating a human embryonic stem cell line carrying a naturally occurring disease-causing mutation in a genomic polynucleotide thereof; or an isolated population of cells consisting of human embryonic stem cells carrying a disease-causing mutation in a genomic polynucleotide thereof as described above, even with respect to SEQ ID NO:24.

Withdrawal of the rejection is respectfully requested.

In view of the above arguments and remarks, Applicants believe they have overcome the 35 U.S.C. § 103 rejections.

Support for claim amendments

Claim 52: Support for the amendments can be found in Page 3, line 30 in the instant application as filed.

Claim 74: Support for the amendments can be found in Page 9, lines 13-15 in the instant application as filed.

Claim 85: Support for new claim 85 can be found in Page 14 (lines 21-23) and Page 23 (lines 21-30) in the instant application as filed.

Claims 86-100: Support for new claims 86-100 can be found in Pages 4-7 in the instant application as filed.

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In view of the above amendments and remarks it is respectfully submitted that claims 52, 55, 57-60, 74, 75, 78-100 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: January 4, 2010

Enclosures:

- Petition for Extension (One Month)
- Request for Continued Examination (RCE)
- References: 1) Castellani et al 2006;
  2) Knezevic et al 2007

Genet Test. 2007 Summer;11(2):133-8.

Analysis of cystic fibrosis gene mutations and associated haplotypes in the Croatian population.

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The aim of this study was to reveal the CFTR gene mutation status in the Croatian population as well as to establish the haplotypes associated with cystic fibrosis (CF) and those associated with specific gene mutations. A total of 48 unrelated CF patients from Croatia were examined. Among 96 tested alleles, we found nine different mutations: DeltaF508, 58.33%; G542X, 3.12%; N1303K, 2.08%; R1162X; 621 + 1G --> T; G85E; Y569C; E585X; and S466X, 1.04%. Analysis of three polymorphic loci revealed 15 different haplotypes. Two of them (21-23-13 and 21-17-13) occurred with a higher frequency (40% and 24%). Both of these haplotypes also carried a CFTR gene mutation (DeltaF508 or G542X) on 27 out of 32 chromosomes. Among 12 (of all together 29) CF alleles on which no mutations were found, we detected 10 different haplotypes. Because there are still no published data on the distribution of polymorphic loci in Croatia, nor haplotypes associated with mutations in the CFTR gene, our results greatly contribute to knowledge regarding the genetic background of CF in this region.

PMID: 17627383 [PubMed - indexed for MEDLINE]

J Cyst Fibros. 2006 Dec;5(4):229-35. Epub 2006 May 18.

The genetic background of osteoporosis in cystic fibrosis: association analysis with polymorphic markers in four candidate genes.

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BACKGROUND: Reduced Bone Mass Density (BMD) is frequent in Cystic Fibrosis (CF). Potentially, other genes than the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene may contribute to the bone phenotype variability in CF patients. METHODS: Four candidate genes likely associated with BMD variability were studied: the vitamin D receptor (VDR) gene, the estrogen receptor alpha (ESR1), the calcitonin receptor (CALCR) and the type I alpha 1 collagen (COL1A1) gene. A complete bone and CF evaluation was obtained for 82 subjects (39 m, 43 f): 15 had normal BMD (group 1), 46 were osteopenic (group 2), and 21 were osteoporotic (group 3). RESULTS: No statistical difference was found among the three groups for age, sex, pancreatic status, and vertebral fractures, nor for any of the biochemical markers. Weight, Body Mass Index (BMI), and FEV1, scored significantly worse in the two groups with the lowest T score. The CFTR mutations R1162X and F508del were more frequent in patients with lower BMD (p=0.044 and p=0.071). There was no significant difference in the distribution of the five marker genotypes among the 3 groups defined according to the unadjusted or adjusted (BMI and FEV1) BMD T score. No significant correlation was found between the VDR, CALCR, or COL1A1 gene polymorphisms and reduced BMD values. The individual ESR1 PvuII-XbaI haplotype C-A is associated to elevated u-calcium levels whereas the haplotype T-A is associated to lower values (p=0.00251). CONCLUSIONS: There was no evidence that the genes under study, with the possible exception of ESR1 gene variants, may modulate bone phenotype in CF.

PMID: 16713399 [PubMed - indexed for MEDLINE]